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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,015	08/04/2008	Eric T. Ahrens	CAMU-P01-002	4194

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ROPES & GRAY LLP
IPRM - Floor 43
PRUDENTIAL TOWER
800 BOYLSTON STREET
BOSTON, MA 02199-3600

EXAMINER	
SAMALA, JAGADISHWAR RAO	
ART UNIT	**PAPER NUMBER**
1618	

NOTIFICATION DATE	DELIVERY MODE
03/15/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatentMail@ropesgray.com
USPatentMail2@ropesgray.com

Office Action Summary	Application No.	Applicant(s)	
	10/586,015	AHRENS, ERIC T.	
	Examiner	Art Unit	
	JAGADISHWAR R. SAMALA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,45,57 and 69-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32,45,57 and 69-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/22/2008 and 01/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group III in the reply filed on 01/05/2011 is acknowledged. Applicant requests rejoinder of Group IV, since Groups III and IV share is directed to methods of administering cells labeled ex vivo with a fluorocarbon imaging reagent to a subject and detecting said cells by MRI. This is found persuasive and accordingly Group IV, claim 57 as rejoined for examination.

- Claims 32, 45 and 57 has been amended.
- Claims 1-32 and 65-68 have been canceled.
- Claims 69-88 have been added.
- Claims 32, 45, 57 and 69-88 are pending in the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 02/22/2008 and 01/22/2009 was noted and the submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

The drawings were received on 07/14/2006. These drawings are acknowledged.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 32, 45, 57, 69-77, 81-82 and 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Philips (US 4,935,223) in view of Walters (US 5,460,800) and Lanza et al US 5,690,907).

Claims are drawn to method for detecting a cell in a subject, comprising: administering to the subject a cell that is labeled with a fluorocarbon imaging agent and examining at least a portion of the subject by a nuclear magnetic resonance technique, thereby detecting a labeled cell in the subject.

Philips teaches a process for the labeling of viable eukaryotic cells and administering the labeled cells to a patient and monitoring the localization of the labeled material. Imaging techniques include positron emission tomography, magnetic resonance imaging, and standard x-ray camera imaging (abstract and col. 7 lines 50-

55). The labeling material (99mTc or 99Tc are ideal scintigraphic imaging agents) is preferably dissolved in saline and is added to the cell suspension. Additional disclosure includes that a number of different labeling materials are within the scope, radioisotopes and paramagnetic agents are preferred labeling material.

Philips fails to teach perfluorocarbon imaging agents, particles of fluorocarbon and additional functional moiety.

Walters teaches a method for labeling and visualizing cells and tissue by administering a composition comprising a physiologically acceptable fluorocarbon liquid and a visualizable label such as a chromophore or fluorescent dye (abstract). The fluorocarbons may be used in cell culture applications, or more importantly, in vivo. Fluorocarbon emulsions may be administered intravenously, intraperitoneally, subcutaneously, or directly into a lymphatic vessel (col. 3 lines 59+). Fluorocarbons include perfluoroalkylated ethers or polyethers, such as $(CF_3)CFO(CF_2CF_2)_2OCF(CF_3)_2$, $(CF_3)_2CFO(CF_2CF_2)OCF(CF_3)$, $(CF_3)CFO(CF_2CF_2)F$, and other variously modified mixed fluorocarbon-hydrocarbon compounds are also encompassed within the broad definition of "fluorocarbon" materials (col. 2 lines 51 +). The emulsifier used in preparing the emulsion includes pluronic, nonionic surfactant, fluorinated surfactants or phospholipids emulsifiers (col. 3 lines 3-10). Additional disclosure includes that fluorescent visualization of the fluorocarbon could facilitate surgical resection of tumors.

Lanza teaches a method for ligand-based binding of lipid encapsulated particles to molecular epitopes on a surface in vivo or in vitro, comprising lipid encapsulated particles activated with a biotin activating agent, whereby the ligand is conjugated to the

particles. The conjugate is effective for imaging (abstract). The lipid encapsulated particles constituted by a perfluorocarbon emulsion, and the particle size range between 0.05 to 5 microns (col. 6 lines 40-45). Further Lanza teaches that various fluorocarbon emulsions may be employed including those in which the fluorocarbon is a fluorocarbon-hydrocarbon, a fluoroalkylated ether, polyether or crown ether (col. 5 lines 65+). Additional disclosure include that perfluorocarbon emulsions are particularly well suited for biomedical applications, are known to stable, biologically inert and readily metabolized, and their circulatory half-life (4-8 hrs) advantageously exceeds that of other agents (col. 5 lines 55+).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate fluorocarbon imaging agent into the viable cells as taught by Philips. The person of ordinary skill in the art would have been motivated to make those modifications because both Walter and Lanza teaches that that perfluorocarbon emulsions are particularly well suited for biomedical applications, are known to stable, biologically inert and readily metabolized, and their circulatory half-life (4-8 hrs) advantageously exceeds that of other agents (Lanza, Col. 5 lines 55+). Also, perfluorocarbons have been used to date in a wide variety of biomedical applications, including use as artificial blood substitutes. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success because both cited reference teach methods and compositions which are capable of targeting and altering the echogenic properties of a tissue surface for improved and specific identification of pathological processes.

Claims 32, 78-80 and 83-85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Philips (US 4,935,223) in view of C. Wilhelm et al (Eur. Biophys. J 31, 118-125, 2002) and Schweighardt et al (US 5,196,348).

Claims are drawn to method for detecting a cell in a subject, comprising: administering to the subject a cell that is labeled with a fluorocarbon imaging agent (perfluor-15-crown-5-ether) and examining at least a portion of the subject by a nuclear magnetic resonance technique, thereby detecting a labeled cell in the subject, wherein the cell is a dendritic cell.

Philips teaches a process for the labeling of viable eukaryotic cells and administering the labeled cells to a patient and monitoring the localization of the labeled material. Imaging techniques include positron emission tomography, magnetic resonance imaging, and standard x-ray camera imaging (abstract and col. 7 lines 50-55). The labeling material (99mTc or 99Tc are ideal scintigraphic imaging agents) is preferably dissolved in saline and is added to the cell suspension. Additional disclosure includes that a number of different labeling materials are within the scope, radioisotopes and paramagnetic agents are preferred labeling material.

Philips fails to teach dendritic cell and perfluor-15-crown-5-ether.

Wilhelm teaches a method to quantify the uptake of magnetic nanoparticles in biological cells. Particle uptake in dendritic cells is quantified for different iron concentration and incubation time. In Table 2 the number of particles internalized per cell is given together with its deviation obtained from the magnetophoresis distribution

(page 123). Additional disclosure includes that the modern MRI technique is to track in vivo the distribution and motion of specific cells and eventually to recover magnetically the labeled cells from organs (page 118).

Schweighardt teaches a method and compositions for improving magnetic resonance spectra of body organs and tissues using fluorocarbons such as perfluoro-15-crown-5-ether having enhanced signal to noise response ratios and having high and diagnostically useful NMR (nuclear magnetic resonance) signal response to the presence of oxygen (abstract). The fluorine-containing agent can be administered within an organ, tissue, blood vessel or cavity of a mammal. After administration, the desired tissue can be biopsied and analyzed by 19F-NMR spectrum (col. 6 lines 46-60). Additional disclosure includes that perfluoro-15-crown-5-ether does not form embolisms and does not precipitate out of emulsion when administered to a mammal in an effective concentration sufficient for unexpectedly high signal to noise response ratios in magnetic resonance spectroscopy, particularly for diagnostic techniques.

It would have been obvious to one ordinary skill in the art at the time the invention was made to incorporate perfluoro-15-crown-5-ether into Philips's method of labeling cells. The person of ordinary skill in the art would have been motivated to make those modifications because Schweighardt teaches that use of perfluoro-15-crown-5-ether provides the multiplied effect of 20 identically electronically and/or magnetically situated fluorine atoms. The particular chemical structure of fluorine's provides a uniquely sharp signal when using nuclear magnetic resonance imaging in a biocompatible fluorine-containing agent. The perfluoro-15-crown-5-ether does not form

embolisms and does not precipitate out of emulsion when administered to a mammal in an effective concentration sufficient for unexpectedly high signal to noise response ratios in magnetic resonance spectroscopy, particularly for diagnostic techniques for determination of oxygen in organs, particularly the spaces surrounding and involved in tissue, tumors or cavities. Therefore, one of ordinary skill in the art would have had a reasonable expectation of success because Schweighardt teaches methods and compositions for improving magnetic resonance spectra of body organs and tissues using fluorochemicals having unexpectedly enhanced signal to noise response ratios and having an unexpectedly high and diagnostically useful NMR signal response to the presence of oxygen. This provides the unique non-intrusive diagnostic capabilities of perfluoro crown ethers as a diagnostic technique.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29

USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 32, 45, 57 and 69-88 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 15-18, 20, 25-27, and 28-30 of copending Application No. 11/787,521. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a method of detecting a cell in a subject, the method comprising; administering to the subject a cell that is labeled with a fluorocarbon imaging agent; and examining at least a portion of the subject by a nuclear magnetic resonance technique. Both sets of claims include limitations that the component includes perfluoro-crown-ether imaging agent and dendritic cells. Accordingly, the scope of the copending claims overlap and thus they are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAGADISHWAR R. SAMALA whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. R. S./ /Jake M. Vu/

Examiner, Art Unit 1618 Primary Examiner, Art Unit 1618